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Enoxacin Penetration into Human Prostatic Tissue

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Concurrent enoxacin concentrations in serum and prostatic tissue were determined in 14 patients. The mean ratios of enoxacin concentration in tissue over concentration in serum were 1.4 ± 0.2 (standard error of the mean). The levels in serum and prostatic tissue were above the MICs for most urinary pathogens.

Enoxacin, a new quinolone derivative which has good antimicrobial activity against most urinary tract pathogens, including gram-negative and gram-positive microorganisms (4–6), appears to be a promising agent for the treatment of urinary tract infections (6). In this study, the penetration of enoxacin into prostatic tissue was evaluated in patients undergoing prostatectomy.

Fourteen patients received two 200-mg capsules of enoxacin 1 to 2 h before being called for surgery. Table 1 summarizes the data for these patients. They were aged 55 to 78 years, with a mean of 65 years. The mean weight was 77.3 kg (63.6 to 91.6 kg). Surgical procedures included 13 transurethral resections in 12 patients with benign prostatic hypertrophy and 1 patient with stage 2 prostatic adenocarcinoma; and a suprapubic prostatectomy in 1 patient with benign prostatic hypertrophy. Serum was taken at the time of induction of anesthesia, when tissue was sampled, and at the end of surgery. Urine samples were collected before the antibiotic was given to the patient and from 0 to 12, 12 to 24, and 24 to 48 h after dosage.

As previously described for norfloxacin (3), enoxacin levels were determined by using a microbiological assay with Mueller-Hinton agar seeded with *Klebsiella pneumoniae* MB 480 derived from ATCC 10031 as the test microorganism. Urine samples were diluted 1:2 in 0.1 N hydrochloric acid to dissolve all drug crystals and then in 1% phosphate buffer (pH 6.0) as needed. Standards were prepared in pooled serum for serum and in 1% phosphate buffer (pH 6.0) for urine. Prostatic tissues were rinsed three times in saline solution, sponged, and weighed. Tissues were then finely chopped with a scalpel and incubated at 37°C for 6 h in a known volume of enzyme solution (collagenase [40 mg%] and hyaluronidase [100 mg%] in 1% phosphate buffer; pH 6.0) to facilitate homogenization, the latter being done at 4°C with a VirTis 45 homogenizer (VirTis Research Equipment, Gardiner, N.Y.). To ensure that this procedure did not influence our results, various concentrations of enoxacin were incubated for 6 h at 37°C in the enzymatic solution. The enoxacin recovery after incubation was 98.4 ± 0.9 (standard error of the mean)%. Standard curves were prepared by using a pool of prostatic tissue containing no antibiotics prepared as described previously (2). All samples (urine, tissue, and serum) were assayed in triplicate and incubated at 28°C overnight before inhibition zones were measured (3). Lowest levels of detection were 0.4 μg ml^{-1} in serum and 1.2 μg g^{-1} in prostatic tissue.

A total of 32 serum samples (7 taken at the time of anesthesia administration, 14 taken at the time of tissue extraction ± 10 min, and 11 taken at the end of surgery), 122 urine samples (14 taken before dosage; 4 taken at the time of tissue extraction; and 28, 25, and 51 taken, respectively, 0 to 12, 12 to 24, and 24 to 28 h after the administration of enoxacin), and 14 prostatic tissue samples were analyzed.

The microbiological activities of enoxacin at the time of tissue extraction varied from 0.4 to 2.8 μg ml^{-1} in serum and from 24.4 to 167.3 μg ml^{-1} in urine (Table 1). Mean levels (± standard error of the mean) of 13.5 ± 2.5, 18.9 ± 5.1, and 12.6 ± 2.2 μg of enoxacin ml^{-1} were detected in the urine samples collected over 0 to 12, 12 to 24, and 24 to 48 h after drug administration. Respectively, 18.2 ± 2.4, 22.5 ± 3.7, and 8.3 ± 1.3% of the dose were recovered in urine over these periods. No antibiotics were detected in any of the urine samples taken before the administration of enoxacin.

Enoxacin was detectable in 10 of the 13 prostatic specimens obtained by transurethral resection. The mean concentration in tissue was 2.2 ± 0.3 μg g^{-1}. Although the antibiotic was undetectable in the tissue obtained by suprapubic prostatectomy, the concentrations in the patient's serum and urine at the same time were 1.5 and 52.8 μg ml^{-1}. All the patients tolerated the drug very well, and no side effect was noted.

The present study demonstrates that enoxacin, which is now used in clinical trials in upper and lower urinary tract infections (8), penetrates prostatic tissue. Indeed, the mean ratio of enoxacin concentration in tissue over concentration in serum was 1.4 ± 0.2. The concentrations in urine and the amount of drug recovered over 24 h were lower than those reported in other studies (7–9). This can be explained in part by the dilution of the urine caused by vesical irrigation after prostatic surgery and also by the diminished renal excretion due to the old age of our patients. In humans, five active metabolites of enoxacin have been found in the urine with the use of the high-pressure liquid chromatography method. Of the total dose of enoxacin, 39.5 to 47.8% is excreted unchanged in the urine and 14% is the oxo-metabolite which possesses about one-tenth the antimicrobial activity of the parent drug (Investigator's Brochure: Comprecin [Enoxacin], Warner-Lambert/Parke-Davis Pharmaceutical Research, February 1987). There might have been some minor interference with the bioassay, so that we cannot exclude the possibility that we overestimated the concentrations in the urine.

Thus, this investigation suggests that this antibiotic, as well as other quinolones (1), readily diffuses from serum into prostatic tissue. Its low protein binding (35%) and its two pK_as may favor entrapment in the human prostatic environment, which is more acid than serum with a pH of 7.28 ±

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TABLE 1. Enoxacin concentrations in urine, serum, and prostatic tissue

Patient no.	Age (yr)	Wt (kg)	Sampling time after dose (h:min)	Concn in:		Tissue/serum concn ratio	Concn in urine ($\mu g\ ml^{-1}$)
				Prostate ($\mu g\ g^{-1}$)	Serum ($\mu g\ ml^{-1}$)		
12	74	78.3	0:55	1.6	2.8	0.6	NS[a]
5	55	87.0	1:40	1.4	1.9	0.7	NS
3[b]	64	91.6	1:55	<1.2	1.5		52.8
11	67	76.0	2:10	<1.2	0.8		24.4
6	71	86.4	2:20	1.4	2.8	0.5	NS
4	58	74.0	2:48	4.5	1.8	2.5	NS
7	57	75.0	3:02	2.1	1.5	1.4	NS
8	70	66.0	4:37	<1.2	0.4		NS
9	58	76.0	5:00	1.5	2.0	0.8	NS
1	78	63.6	5:15	<1.2	1.7		136.2
10	61	79.5	5:45	1.6	0.7	2.3	NS
2[c]	67	68.0	6:00	1.3	1.2	1.1	167.3
13	66	89.0	6:20	3.2	1.4	2.3	NS
15	64	72.2	8:00	3.2	1.4	2.3	NS

[a] NS, No specimen.
[b] Suprapubic prostatectomy.
[c] Stage 2 prostatic adenocarcinoma.

0.04 in the normal individual (5). Of greatest importance is the observation that the levels of enoxacin in serum, prostatic tissue, and urine over 72 h were way over the MICs for most urinary pathogens (4–6), indicating that this new quinolone may be effective in the treatment of severe prostatitis and pyelonephritis.

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